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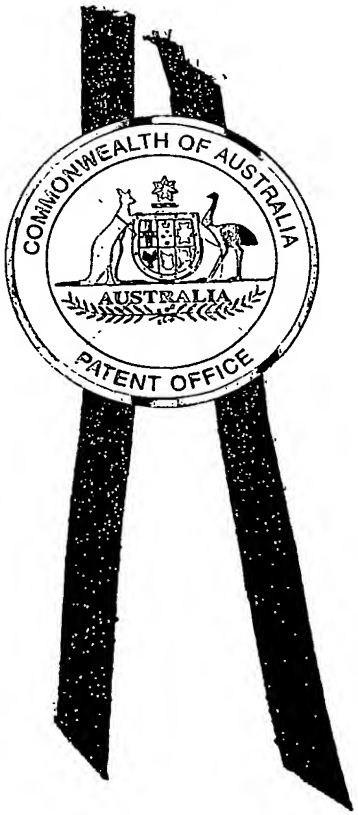

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PROVISIONAL SPECIFICATION

Invention title: **Phosphate Derivatives**

The invention is described in the following statement:

Phosphate Derivatives

Field of the invention

The invention relates to substances having improved water solubility. More particularly, the present invention relates to phenolic hydroxyl compounds having improved water solubility.

Background of the invention

In this specification, where a document, act or item of knowledge is referred to or discussed, this reference or discussion is not an admission that the document, act or item of knowledge or any combination thereof was at the priority date:

(a) part of common general knowledge; or

(b) known to be relevant to an attempt to solve any problem with which this specification is concerned.

Whilst the following discussion relates to anaesthetics, it will be understood that the invention has applications to other compounds containing phenolic hydroxyl groups, where improved water solubility, rapid activity or improved delivery is desired, for example; with adrenaline (CAS 51-43-4 & 99-45-6) and analgesics (CAS 36322-90-4).

An ideal anaesthetic drug would induce anesthesia smoothly and quickly, then permit rapid patient recovery upon cessation. The drug would also be safe to use and free of side effects, but as no single agent possesses all these attributes, combinations of drugs are often used in modern practice.

Propofol is an extremely important intravenous induction agent as it produces anesthesia at a rate similar to intravenous barbiturates but recovery is more rapid. Patients report feeling better in the immediate postoperative period and are able to ambulate sooner in comparison to other agents. Postoperative vomiting and nausea is uncommon as propofol is reported to have anti-emetic actions. For these reasons propofol is a popular drug especially in day surgery where it is used both as an induction and maintenance anesthetic.

An important disadvantage of propofol arises from its lipid solubility, requiring the compound to be delivered in other more soluble lipidic carriers that improve dissolution such as medium chain length triglyceride (Cremophor), oil in water emulsion

(Intralipid), polyoxyl 35 castor oil (hydrogenated castor oil) or other lipidic emulsion systems.

Hypersensitivity reactions have been reported with propofol. These include hypotension, flushing and bronchospasm, that are largely thought to be due to the lipid vehicle Cremaphor. Although side effects using intralipid emulsions are reported to be lower, an improved delivery strategy that eliminates the need to use an emulsion system needs to be developed.

Propofol phosphate is a water soluble derivative of propofol. Intravenous administration of propofol phosphate would be expected to convert to the parent compound via the action of plasma and tissue phosphatases such as alkaline phosphatase. *In vitro* use of propofol phosphate does not however induce anesthesia and does not release the parent drug because the phosphate group is slow to hydrolyse.

Therefore, the need for an improved water soluble delivery system for phenolic hydroxy compounds where the pro-drug rapidly converts to the parent drug remains.

Summary of the invention

Surprisingly, it has been found that reacting a phosphate derivative of a phenolic hydroxy compound with an alkyl α:ω dialdehyde or a sugar-like polyhydroxy dialdehyde to form a hemiacetal, then reducing the terminal aldehyde to a hydroxyl group and phosphorylating the group, gave compounds that hydrolysed under biological conditions to release the parent compound thus producing rapid activity.

According to a first aspect of the invention, there is a drug delivery system for compounds having phenolic hydroxy groups comprising the reaction product of the following steps:

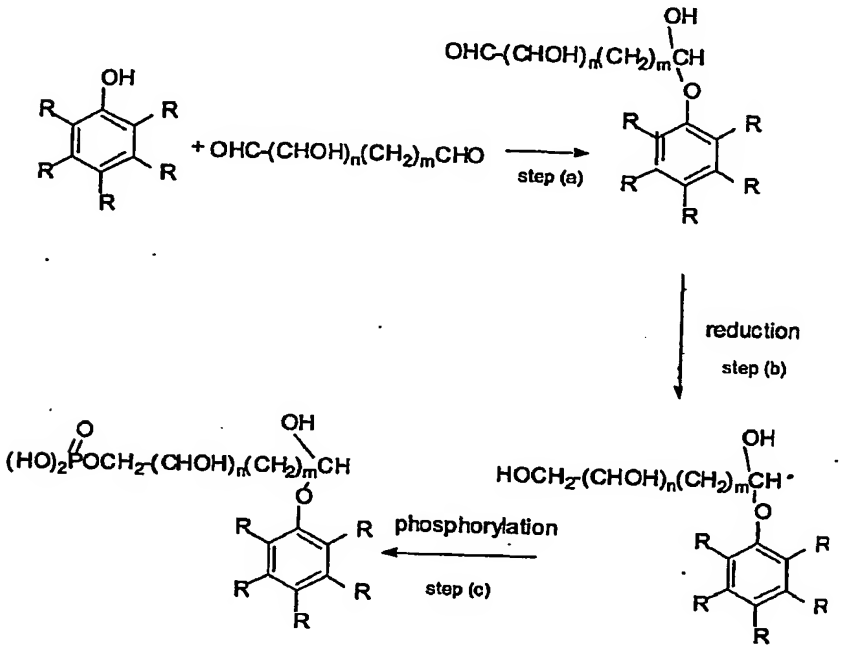
(a) reacting a phosphate derivative of a phenolic hydroxy compound with an alkyl α:ω dialdehyde or a sugar-like polyhydroxy dialdehyde to form a hemiacetal;

(b) reducing the terminal aldehyde group on the product from step (a) to a hydroxyl group; and

(c) phosphorylating the hydroxyl group formed in step (b).

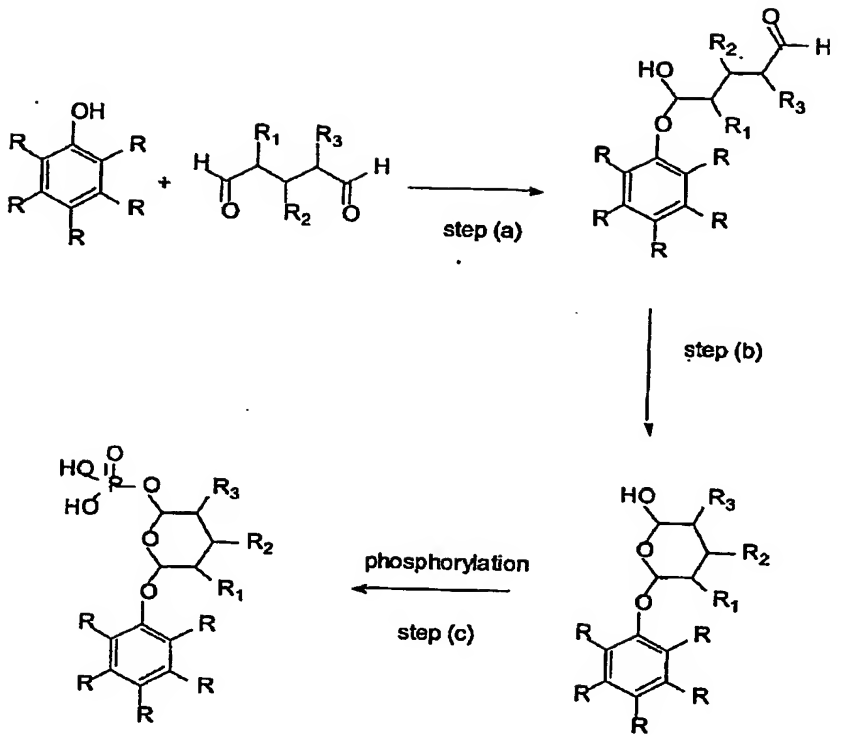
The following Reaction Schemes 1 and 2 illustrate the three reaction steps according to the first aspect of the invention. In both of the schemes, each R may be either H or an alkyl group.

Reaction Scheme 1



n = 0-8, m=0-8

Reaction Scheme 2



R_1, R_2, R_3 = H or OH

According to a second aspect of the invention, there is provided a delivery system comprising the reaction product of:

(a) one or more compounds according to the first aspect of the invention, and

(b) a complexing agent selected from the group comprising amphoteric surfactants, cationic surfactants, amino acids having nitrogen functional groups and proteins rich in these amino acids.

Where used herein the term "phosphate derivatives" refers to compounds covalently bound by means of an oxygen to the phosphorus atom of a phosphate group. The phosphate derivative may exist in the form of a free phosphate acid, a salt thereof, a di-phosphate ester thereby including two phenolic hydroxy compound molecules, a mixed ester including one phenolic hydroxy compound and another phenolic hydroxy compound, and a phosphatidyl compound wherein the free phosphate oxygen forms a bond with an alkyl or substituted alkyl group.

Suitable complexing agents for use in the invention may be selected surfactants chosen from classes including from alkyl amino/amido betaines, sultaines, phosphobetaines, phosphitaines, imidazolimum and straight chain mono and dicarboxy ampholytes, quaternary ammonium salts, and cationic alkoxylated mono and di-fatty amines; and amino acids having nitrogen functional groups and proteins rich in these amino acids. Preferred complexing agents are N-lauryl imino di-propionate and arginine.

Suitable amino acids having nitrogen functional groups for use in the invention include glycine, arginine, lysine and histidine. Proteins rich in these amino acids may also be used as complexing agents, for example, casein. These complexing agents are used when the composition needs to be delivered by other routes of administration including but not limited to inhalation, oral ingestion, dermal application, eye drops or suppositories.

The amphoteric surfactants may be ampholytic surfactants, that is, they exhibit a pronounced isoelectric point within a specific pH range; or zwitterionic surfactants, that is, they are cationic over the entire pH range and do not usually exhibit a pronounced isoelectric point. Examples of these amphoteric surfactants are tertiary substituted amines, such as those according to the following formula:

$$NR^1R^2R^3$$

wherein R^1 is chosen from the group comprising straight or branched chain mixed alkyl radicals from C6 to C22 and carbonyl derivatives thereof.

R^2 and R^3 are independently chosen from the group comprising H, CH_2COOX, $CH_2CHOHCH_2SO_3X$, $CH_2CHOHCH_2OPO_3X$, CH_2CH_2COOX, CH_2COOX, $CH_2CH_2CHOHCH_2SO_3X$ or $CH_2CH_2CHOHCH_2OPO_3X$ and X is H, Na, K or alkanolamine provided that R^2 and R^3 are not both H.

In addition, when R^1 is RCO then R^2 may be CH_3 and R^3 may be $(CH_2CH_2)N(C_2H_4OH)$-H_2COPO_3 or R^2 and R^3 together may be $N(CH_2)_2N(C_2H_4OH)CH_2COO$-.

Commercial examples are DERIPHAT sold by Henkel/Cognis, DEHYTON sold by Henkel/Cognis, TEGOBETAINE sold by Goldschmidt and MIRANOL sold by Rhone Poulenc.

Cationic surfactants, such as quaternary ammonium compounds, will also form complexes with phosphorylated derivatives of drug hydroxy compounds such as tocopheryl phosphates. Examples of cationic surfactants include the following:

(a) $RN^+(CH_3)_3\ Cl^-$

(b) $[R_2N^+CH_3]_2\ SO_4^{2-}$

(c) $[RCON(CH_3)CH_2CH_2CH_2N^+(CH_3)_2C_2H_4OH]_2\ SO_4^{2-}$

(d) Ethomeens: $RN[(CH_2CH_2O)_x\ CH_2OH][(CH_2CH_2O)_y\ CH_2OH]$ wherein x and y are integers from 1 to 50.

wherein R is C8 to C22 straight or branched chain alkyl groups or mixed alkyl groups.

Silicone surfactants including hydrophilic and hydrophobic functionality may also be used, for example, dimethicone PG betaine, amodimethicone or trimethylsilylamodimethicone. For example, ABILE 9950 from Goldschmidt Chemical Co. The hydrophobe can be a C6 to C22 straight -or branched alkyl or mixed alkyl including fluoroalkyl, fluorosilicone and or mixtures thereof. The hydrophilic portion can be an alkali metal, alkaline earth or alkanolamine salts of carboxy alkyl groups or sulfoxy alkyl groups, that is sultaines, phosphitaines or phosphobetaines or mixtures thereof.

Typically, the reaction product of the delivery system of the present invention is made by (1) direct neutralization of the free phosphoric acid ester of propofol with the complexing agents or (2) in-situ blending of mixed sodium salts of the phosphate derivatives of propofol with the complexing agents.

Forms of propofol which may be used in this invention include:

- 2,6-diisopropylphenol (CAS 2078-54-8)
- Propofol phosphate or Phenol, 2,6-bis(1-methylethyl)-, dihydrogen phosphate (9CI) (CAS 18351-38-7)

- Phenol, 2,6-bis(1-methylethyl)-, dihydrogen phosphate, disodium salt (9CI) (CAS 250345-80-3)

The delivery system according to the invention when used in any route of administration (oral, transmucosal, intranasal, transdermal, intravenous) may provide improved water solubility eliminating need for dissolution in lipidic vehicles and side effects associated with these compounds.

Examples

The invention will now be further explained and illustrated by reference to the following non-limiting examples.

Example 1

17.8g (0.1M) of 2,6-di-isopropylphenol was placed in a 100 ml flask with a good agitator. 4.2 g of sodium hydrogen carbonate and 3.4g of sodium carbonate were dissolved in 23.2 g of 50% aqueous gluteraldehyde. This solution was added to the 2,6-di-isopropylphenol with vigorous stirring over a one hour period. Then stirring continued for one hour. The water was evaporated to give the dry hemiacetal derivative of 2,6-di-isopropylphenol (A). A was dissolved in 50 ml of toluene, then 7.8 g of P_4O_{10} was added and the mixture stirred for one hour with the temperature maintained in the range 40 to 60°C. 50 ml of water was carefully added and the mixture stirred for thirty minutes to hydrolyse any pyrophosphates. The toluene phase was separated using a separating funnel and dried to produce 2-(2,6-diisopropylphenoxy)-tetrahydropyran-6-yl , dihydrogen phosphate (I).

Example 2

17.8g (0.1M) of 2,6-di-isopropylphenol was placed in a 100 ml flask with a good agitator. 4.2 g of sodium hydrogen carbonate and 3.4g of sodium carbonate were dissolved in 32.6 g of 50% aqueous trihydroxy pentandial. This solution was added to the 2,6-di-isopropylphenol with vigorous stirring over a one hour period. Then stirring continued for one hour. The water was evaporated to give the dry hemiacetal derivative of 2,6-di-isopropylphenol (B). B was dissolved in 50 ml of toluene, then 7.8 g of P_4O_{10} was added and the mixture stirred for one hour, maintaining the temperature in the range 40 to 60°C. 50 ml of water was carefully added and the mixture stirred for thirty minutes to hydrolyse any pyrophosphates. The toluene phase was separated using a separating

funnel and dried to produce 2-(2,6-diisopropylphenoxy)-3,4,5-trihydroxy tetrahydropyran-6-yl, dihydrogen phosphate (II).

Example 3

17.8g (0.1M) of 2,6-di-isopropylphenol was placed in a 100 ml flask with a good agitator. 4.2 g of sodium hydrogen carbonate and 3.4g of sodium carbonate were dissolved in 12.8 g of 50% aqueous glyoxyal. This solution was added to the 2,6-di-isopropylphenol with vigorous stirring over a one hour period. Then stirring continued for one hour. 3.8 g of sodium borohydride was added and the mixture stirred for one hour. The water was evaporated to give the dry hemiacetal derivative of 2,6-di-isopropylphenol (C). C was dissolved in 50 ml of toluene, then 7.8 g of P_4O_{10} was added and the mixture stirred for one hour, maintaining the temperature in the range 40 to 60°C. 25 ml of water was carefully added and the mixture stirred for thirty minutes to hydrolyse any pyrophosphates. The toluene phase was separated using a separating funnel and dried to produce 2-(2,6-diisopropylphenoxy)-2-hydroxy ethylphosphate (III) .

Example 4

373 g (1 M) of disodium lauryl-imino-dipropionate was dissolved in 2000 ml of deionized water and warmed to 50-60°C to form a clear solution of pH 11-12. 358 g (1 M) of I was added with good agitation to form the disodium lauryl-imino-dipropionate- 2-(2,6-diisopropylphenoxy) tetrahydropyran-6-yl dihydrogen phosphate complex (IV) at a pH of 8-9 as an aqueous solution. The pH may be adjusted by adding appropriate amounts of either component.

Example 5

174 grams of arginine was dissolved in 1000ml of deionized water. 406 g of II was added to this solution with good agitation to yield the arginine 2-(2,6-diisopropylphenoxy)-3,4,5-trihydroxy tetrahydropyran-6-yl dihydrogen phosphate complex (V) as an aqueous solution with final pH of 6.5-7.5.

Example 6

17 g (0.1M) arginine was dissolved into 100ml of deionized water. 31.8 g (0.1M) of III was added to this solution with good agitation to form an arginine 2-(2,6-diisopropylphenoxy)-2-hydroxy ethylphosphate complex (VI) as an aqueous complex with final pH of 6.5-7.5.

Example 7

373 g (1 M) of disodium lauryl-imino-dipropionate was dissolved in 200 ml of deionized water and warmed to 50-60°C to form a clear solution of pH 11-12. 358 g (1 M) of I was added with good agitation to form the disodium lauryl-imino-dipropionate 2-(2,6-diisopropylphenoxy) tetrahydropyran-6-yl dihydrogen phosphate complex (VII) at a pH of 8-9 as an aqueous solution. The pH may be adjusted by adding appropriate amounts of either component. The solution was then freeze dried for 24 hours to yield the complex as a dry powder.

Example 8

174 grams of arginine was dissolved in 200 ml of deionized water. 406 g of II was added to this solution with good agitation to yield the 2-(2,6-diisopropylphenoxy)-3,4,5-trihydroxytetrahydropyran-6-yl dihydrogen phosphate arginine complex (VIII) with final pH of 6.5-7.5. The solution was then freeze dried for 24 hours to yield the complex as a dry powder.

Example 9

17 g (0.1M) arginine was dissolved into 20ml of deionized water. 31.8 g (0.1M) of III was added with good agitation to form an arginine 2-(2,6-diisopropylphenoxy)-2-hydroxy ethylphosphate complex (IX) as an aqueous complex with final pH of 6.5-7.5. The solution was then freeze dried for 24 hours to yield the complex as a dry powder.

Example 10

174 grams of arginine was dissolved in 200 ml of deionized water. 358 g of I was added to this solution with good agitation to yield the 2-(2,6-diisopropylphenoxy)-tetrahydropyran-6-yl dihydrogen phosphate arginine complex (X) with final pH of 6.5-7.5. 0.3M 2,6-di-isopropylphenol was added and fully emulsified with a high sheer agitator. The solution was then freeze dried for 24 hours to yield a product being a mixture of the complex and free 2,6-di-isopropylphenol that when used intravenously acted as an anaesthetic. The free 2,6-di-isopropylphenol is available for immediate anaesthetic action in an emulsified state and the complex for slower delivery of the 2,6-di-isopropylphenol after hydrolysis.

The word 'comprising' and forms of the word 'comprising' as used in this description does not limit the invention claimed to exclude any variants or additions.

Modifications and improvements to the invention will be readily apparent to those skilled in the art. Such modifications and improvements are intended to be within the scope of this invention.

Vital Health Sciences Pty Ltd

15 April 2003